VOLUME 24 · NUMBER 7 · MARCH 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Addition of Epirubicin As a Third Drug to Carboplatin-Paclitaxel in First-Line Treatment of Advanced Ovarian Cancer: A Prospectively Randomized Gynecologic Cancer Intergroup Trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens

*Andreas du Bois, Beatrice Weber, Justine Rochon, Werner Meier, Alain Goupil, Sigrid Olbricht, Jean-Claude Barats, Walther Kuhn, Hubert Orfeuvre, Uwe Wagner, Barbara Richter, Hans-Joachim Lueck, Jacobus Pfisterer, Serban Costa, Willibald Schroeder, Rainer Kimmig, and Eric Pujade-Lauraine*

From the Department of Gynecology & Gynecologic Oncology, HSK Dr Horst Schmidt Klinik Wiesbaden; Department of Gynecology, St Vincentius Khs Karlsruhe; KKS Marburg, Coordination Center for Clinical Trials, Department of Gynecology and Obstetrics, Evangelisches Krankenhaus, Duesseldorf; Department of Gynecology and Obstetrics, Medizinische Akademie, Magdeburg; Department of Gynecology and Obstetrics, University Muenchen rechts der Isar; Department of Gynecology, University Hospital, Tuebingen; Department of Gynecology and Obstetrics, University of Dresden, Dresden; Department of Gynecologic Oncology, Medizinische Hochschule, Hannover; Department of Gynecology and Obstetrics, University Hospital of Schleswig-Holstein Campus Kiel; Department of Gynecology and Obstetrics, University of Frankfurt, Frankfurt; Department of Gynecology and Obstetrics, Rheinisch-Westfaelische Technische Hochschule, Aachen; Department of Gynecology and Obstetrics, University Muenchen-Großhadern, Germany; Department of Oncology, Centre Alexis-Vautrin, Vandoeuvre-les-Nancy; Department of Oncology, Centre René Huguenin, Saint-Cloud; Department of Oncology-Hematology, Hôpitaux Civils, Colmar; Department of Oncology-Hematology, Hôpital Fleyriat, Bourg-en Bresse; and Department of Oncology, Hôpital Hôtel-Dieu, Paris, France.

Submitted July 7, 2005; accepted December 14, 2005.

Supported by (and study medication provided by) Bristol-Myers Squibb and Pharmacia-Upjohn.

Presented in part at the 40th Annual Meeting of the Society of Clinical Oncology, June 5-8, 2004, New Orleans, LA.

The drugs and regimens evaluated in this purely scientific trial may not be registered for this indication in some countries.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Andreas du Bois, MD, HSK Dr Horst Schmidt Klinik, Department of Gynecology & Gynecologic Oncology, Ludwig-Erhard-Str 100, D-65199 Wiesbaden, Germany; e-mail: dubois.hsk-wiesbaden@uumail.de.



0732-183X/06/2407-1127/$20.00

DOI: 10.1200/JCO.2005.03.2938

## ABSTRACT

### Purpose
Despite the progress that has been achieved, long-term survival rates in patients with advanced ovarian cancer are still disappointing. One attempt to improve results could be the addition of non–cross-resistant drugs to platinum-paclitaxel combination regimens. Anthracyclines were among the candidates for incorporation as a third drug into first-line regimens.

### Patients and Methods
We performed a prospectively randomized phase III study comparing carboplatin-paclitaxel (TC; area under the curve 5/175 mg/m$^2$, respectively) with epirubicin 60 mg/m$^2$ added to the same combination (TEC) in previously untreated patients with advanced epithelial ovarian cancer. All drugs were administered intravenously on day 1 of a 3-week schedule for a planned minimum of six courses.

### Results
Between November 1997 and February 2000, 1,282 patients were randomly assigned to receive either TC (635 patients) or TEC (647 patients), respectively. Grade 3/4 hematologic and some nonhematologic toxicities (nausea/emesis, mucositis, and infections) occurred significantly more frequently in the TEC arm. Accordingly, quality-of-life analysis showed inferiority of TEC versus TC. Median progression-free survival time was 18.4 months for the TEC arm and 17.9 months for the TC arm (hazard ratio [HR], 0.95; 95% CI, 0.83 to 1.07; $P = .3342$). Median overall survival time was 45.8 months for the TEC arm and 41.0 months for the TC arm (HR, 0.93; 95% CI, 0.81 to 1.08; $P = .3652$). Similar nonsignificant differences were observed when strata were analyzed separately.

### Conclusion
Addition of epirubicin to TC did not improve survival or time to treatment failure in patients with advanced epithelial ovarian cancer; therefore, it cannot be recommended for clinical use in this population.

*J Clin Oncol 24:1127-1135. © 2006 by American Society of Clinical Oncology*

## INTRODUCTION

Since the publication of two large studies reporting superiority of platinum-paclitaxel compared with the older combination of platinum with alkylating agents,[1,2] this combination has been widely adopted as a new standard first-line treatment for advanced ovarian cancer. Several attempts have been made to optimize this cisplatin-based regimen and two randomized phase III trials demonstrated that carboplatin can be substituted for cisplatin without loss of efficacy.[3,4] However, the substitution of carboplatin for cisplatin resulted in better tolerance and quality of life (QoL) but did not increase long-term survival rates. The impressive median survival rates approaching 5 years that have been reported by these two trials for optimally debulked patients cannot mask the urgent need for more effective treatment in these patients.

Among others, one option for achieving further progress in the first-line treatment of advanced ovarian cancer might be the addition of non–cross-resistant drugs to the two-drug combination of platinum and paclitaxel. Anthracyclines are among the candidates for the third drug. Three meta-analyses showed a survival benefit for platinum-anthracycline based combinations when compared with platinum-based combinations without anthracyclines.[5-7] Furthermore, both doxorubicin (as liposomal formulation) and epirubicin, a doxorubicin analog, have shown activity as second-line treatment even after prior platinum and (in some patients) paclitaxel-containing first-line chemotherapy.[8,9] Consequently, the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) developed a feasible triple-drug regimen combining carboplatin-paclitaxel with epirubicin (TEC) for additional evaluation.[10] Under the auspices of the Gynecologic Cancer Intergroup (GCIG), the German AGO-OVAR and the French Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) performed a prospectively randomized phase III study comparing TEC with carboplatin-paclitaxel (TC) in advanced epithelial ovarian cancer. Some results of this trial were presented at the 40th Annual Meeting of the American Society of Clinical Oncology,[11] and the final results are reported in this article.

## PATIENTS AND METHODS

The study was designed and carried out in accordance with good clinical practice guidelines, German and French drug laws, and the Declaration of Helsinki. Local ethics committee of each participating center in Germany and France approved the study. All patients provided written informed consent before study entry.

### *Eligibility Criteria, Randomization, and Quality Assurance*

Patients with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO)[12] stages IIB to IV ovarian cancer were eligible. Patients had to have undergone radical debulking surgery within 6 weeks of random assignment. All patients had to be at least 18 years of age and were required to have adequate hematologic, renal, and hepatic function, defined as follows: absolute neutrophil count (ANC) of at least 1.5 × 109 cells/L, platelet count of at least 100 × 109 cells/L, serum creatinine and bilirubin of no more than 1.25 × the upper normal limit. Patients were excluded from the study if they had ovarian tumors with low malignant potential; an Eastern Cooperative Oncology Group performance status of more than 2 or a Karnofsky performance status of less than 60%; an estimated glomerular filtration rate (GFR) of less than 60 mL/min; other malignancies; previous chemotherapy, immunotherapy, or radiotherapy for ovarian cancer; severe neuropathy; cardiac arrhythmias; or congestive heart failure. An evaluation of left ventricular ejection fraction had to be performed if patients had any medical cardiac history or clinical performance indicated any signs of heart disease.

Patients were stratified into one of two a priori strata according to residual tumor size and FIGO stage. Stratum 1 contained patients with a residual tumor size of up to 1 cm and had FIGO stage IIB, IIC, or III disease. Stratum 2 contained patients with a residual tumor size of more than 1 cm or had FIGO stage IV disease. Within each stratum, randomization lists for each study center were prepared before the start of the trial using permuted blocks of randomly varying size. Patients were randomly assigned by the responsible study office of each study group. All participating centers were monitored regularly by trained field monitors who checked all of the data collected on case review forms against the medical records including the surgeon's and pathologist's reports for each patient (ie, 100% monitoring). Additional quality assurance measures consisted of double data entry and extensive programmed plausibility checks.

### *Treatment Regimens*

Patients were randomly assigned to receive TC or TEC. Patients in the TC arm received paclitaxel 175 mg/m$^2$ administered intravenously (IV) during 3 hours, followed by carboplatin (area under the time-concentration curve [AUC] 5) administered IV during 30 to 60 minutes. Patients in the TEC arm received epirubicin 60 mg/m$^2$ administered IV during 30 minutes or bolus after having received TC. The carboplatin dose was calculated using the method of Calvert et al[13] in which the required dose is obtained by the following formula: carboplatin dose in milligrams = AUC × (GFR + 25). The GFR was estimated using the Jelliffe formula.[14] Regardless of calculated doses, the maximal absolute dose was limited to 385 mg for paclitaxel, 800 mg for carboplatin, and 130 mg for epirubicin.

Dose reductions were allowed depending on predefined levels of hematologic or nonhematologic toxicity, with dose reduction levels as follows: carboplatin AUC 4 (level −1/level −2); paclitaxel 150 mg/m$^2$ (level −1) or 135 mg/m$^2$ (level −2); and epirubicin 50 mg/m$^2$ (level −1) or 40 mg/m$^2$ (level −2). Any subsequent treatment cycle was delayed when the patient's ANC was less than 1.5 × 109 cells/L or the platelet count was less than 100 × 109 cells/L. Primary prophylaxis using granulocyte colony-stimulating factor (G-CSF) was not allowed; however, supportive G-CSF treatment could be initiated at the discretion of the investigator if the patient's ANC recovery took more than 36 days.

All patients received premedication consisting of a single dose of dexamethasone (20 mg), and both a histamine receptor type 1 and histamine receptor type 2 blocking agent (eg, clemastine 2 mg and cimetidine 300 mg) administered 30 minutes before the start of the paclitaxel infusion. Antiemetic prophylaxis consisted of 5-hydroxytryptamine-3 antagonists and corticosteroids. Chemotherapy cycles were repeated every 3 weeks. Patients with disease progression during therapy discontinued protocol treatment. Patients who achieved partial remission and who exhibited residual tumor after six treatment cycles could receive additional treatment cycles if recommended by the physician.

### *Evaluations and Follow-Up*

Adverse events and toxicities were graded by study investigators according to the National Cancer Institute Common Toxicity Criteria version 2.0.[15] All observed toxicities were recorded continuously; blood chemistry parameters were measured before each treatment cycle and hematologic parameters were measured weekly. QoL was evaluated in the German subcohort using

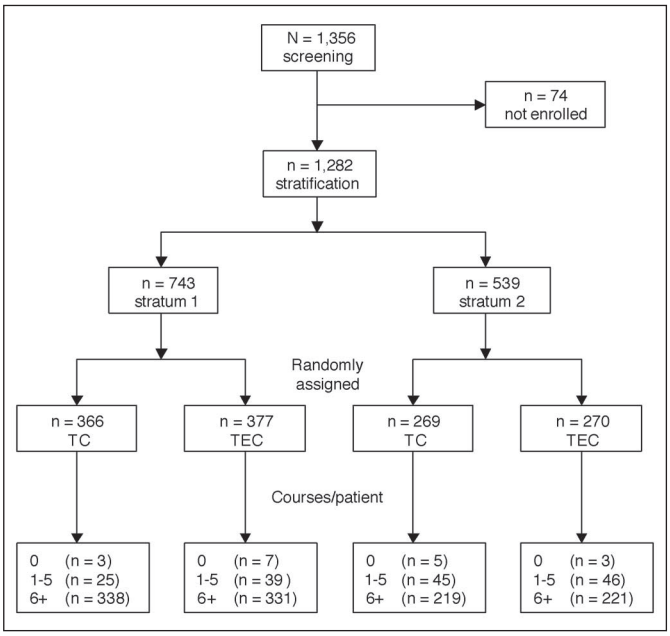


**Fig 1.** Consort diagram. TC, carboplatin-paclitaxel; TEC, carboplatin-paclitaxel plus epirubicin.

**Table 1.** Baseline Patient Characteristics

| Characteristic | TC Arm | | TEC Arm | | Total | |
|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| No. of patients | 635 | 49.5 | 647 | 50.5 | 1,282 | 100.0 |
| Age, years | | | | | | |
| Median | 58 | | 60 | | 59 | |
| Range | 22-79 | | 21-79 | | 21-79 | |
| FIGO stage | | | | | | |
| Unknown | 3 | | 3 | | 6 | |
| IB | 1 | 0.2 | 0 | 0.0 | 1 | 0.1 |
| IIB | 21 | 3.3 | 20 | 3.1 | 41 | 3.2 |
| IIC | 36 | 5.7 | 42 | 6.5 | 78 | 6.1 |
| IIIA | 37 | 5.9 | 36 | 5.6 | 73 | 5.7 |
| IIIB | 69 | 10.9 | 83 | 12.9 | 152 | 11.9 |
| IIIC | 352 | 55.7 | 358 | 55.6 | 710 | 55.6 |
| IV | 116 | 18.4 | 105 | 16.3 | 221 | 17.3 |
| Postoperative residual tumor, cm | | | | | | |
| Unknown | 75 | | 76 | | 151 | |
| ≤ 1 | 388 | 69.3 | 385 | 67.4 | 773 | 68.3 |
| > 1 | 172 | 30.7 | 186 | 32.6 | 358 | 31.7 |
| Stratification | | | | | | |
| Stratum 1* | 366 | 57.6 | 377 | 58.3 | 743 | 58.0 |
| Stratum 2† | 269 | 42.4 | 270 | 41.7 | 539 | 42.0 |
| Histology | | | | | | |
| Unknown | 3 | | 0 | | 3 | |
| Serous/papillary | 461 | 72.9 | 476 | 73.6 | 937 | 73.3 |
| Endometrioid | 56 | 8.9 | 55 | 8.5 | 111 | 8.7 |
| Mucinous | 26 | 4.1 | 37 | 5.7 | 63 | 4.9 |
| Other | 89 | 14.1 | 79 | 12.2 | 168 | 13.1 |
| Histologic grade | | | | | | |
| Unknown | 96 | | 85 | | 181 | |
| 1 | 54 | 10.0 | 53 | 9.4 | 107 | 9.7 |
| 2 | 179 | 33.2 | 204 | 36.3 | 383 | 34.8 |
| 3 | 306 | 56.8 | 305 | 54.3 | 611 | 55.5 |
| ECOG performance status | | | | | | |
| Unknown | 8 | | 9 | | 17 | |
| 0 | 208 | 33.2 | 205 | 32.1 | 413 | 32.6 |
| 1 | 335 | 53.4 | 356 | 55.8 | 691 | 54.6 |
| 2 | 83 | 13.2 | 77 | 12.1 | 160 | 12.7 |
| 3 | 1 | 0.2 | 0 | 0.0 | 1 | 0.1 |

Abbreviations: TC, paclitaxel-carboplatin; TEC, paclitaxel-carboplatin plus epirubicin; FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group.
*FIGO stages IIB-III and residual tumor size ≤ 1 cm.
†FIGO stage IV or residual tumor size of > 1 cm.

global health status/QoL score of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), version 2.0.[16] Patients assessed their own health-related QoL every other treatment cycle, after the last treatment cycle, and every 3 months after cessation of treatment during the first year. QoL responses were evaluated according to the EORTC guidelines.[17] Tumor measurements were made before each treatment cycle by physical examination, before every third treatment cycle by imaging methods in patients with measurable or assessable disease, and after the last treatment cycle. The same tumor assessment methods (ie, ultrasound, x-ray, computed tomography, or magnetic resonance imaging) that were employed for baseline measurement were also used for each repeat evaluation. Tumor response was graded according to the definitions of the WHO.[18] Second-look surgery was not recommended. Follow-up visits were scheduled every 3 months in the first 2 years after cessation of treatment and every 6 months thereafter, for a total follow-up time of 5 years.

### *Statistical Analyses*

The primary outcome measure was overall survival; secondary end points were progression-free survival, response to treatment, toxicity, and QoL. With an estimated 3-year overall survival proportion of 50% in the TC group, the trial aimed to detect an improvement of 8% (to 58%) in the TEC group, with 5% significance (two sided) and 80% power using a stratified log-rank test, which required at least 541 events. Overall survival was defined as the time from random assignment to death as a result of any cause; survivors were censored at the date they were last known to be alive. Progression-free survival was defined as the time from random assignment to disease progression or death as a result of any cause; patients who were still alive without progressive disease at the time of analysis were censored at the date of their last follow-up. Response to treatment was assessed according to WHO criteria. Overall response rate was defined as the number of patients who had a partial or complete response divided by the number of patients with measurable

disease at baseline. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria and were evaluated using the worst score over all courses (set C) and over all courses within patients (set P). Time-to-event data were analyzed using the Kaplan-Meier (KM) method, and the (stratified) log-rank test was used to compare the distributions between groups. KM estimates of potential follow-up were used to quantify the median follow-up time. In addition, hazard ratios (HRs) with 95% CIs were estimated using the Cox proportional hazards model. The stratified Cochran-Mantel-Haenszel test was used for the comparison of categoric data. All *P* values are two sided. Efficacy analyses were performed on all randomly assigned patients (intention-to-treat basis). Patients receiving at least one treatment cycle were qualified for safety analysis. Patients who had completed QLQ-C30 questionnaires for at least three of the four time points (1, baseline; 2, before the second cycle; 3, before the fourth cycle; 4, at end of treatment) were qualified for QoL analysis. The differences of worst respective mean global health score over time points 2 to 4 versus baseline were used as summary measures and compared using the Wilcoxon-Mann-Whitney test. All statistical analyses were done with SAS software (version 8.2; SAS Institute, Cary, NC).

## RESULTS

### Patients

Between November 1997 and February 2000, 1,356 patients were screened by the AGO-OVAR and GINECO study offices. Of these, 74 patients (5.5%) were not enrolled because of low GFR (n = 45), histology of nonepithelial ovarian cancer (n = 10), secondary malignancies (n = 4), surgery more than 6 weeks before study entry (n = 6), wrong FIGO stage (n = 5), or other reasons (n = 4). Of the remaining 1,282 patients, 743 patients fulfilled the criteria for stratum 1 and 539 patients fulfilled the criteria for stratum 2 (Fig 1). After written informed consent was provided, 635 patients were randomly assigned to TC and 647 were randomly assigned to TEC. The treatment arms were well balanced for baseline characteristics (Table 1).

### Treatment Compliance and Toxicity

Overall, 7,516 treatment cycles were administered: 3,806 cycles in the TC arm and 3,710 cycles in the TEC arm. A total of 1,264 patients received at least one treatment cycle. Most patients received at least six treatment cycles: 87.7% in the TC arm and 85.3% in the TEC arm. In all, 103 of the patients receiving TC (16.2%) and 67 of the patients receiving TEC (10.4%) received more than six treatment cycles.

Treatment delays of at least 7 days occurred in 231 of 627 (36.8%) patients in the TC arm and 252 of 637 (39.6%) patients in the TEC arm. This difference did not reach statistical significance.

Overall, 183 (14.5%) of the 1,264 patients received at least one dose reduction. Again, there was a statistically significant difference between the treatment arms in the percentage of patients with at least one dose reduction (9.9% in the TC arm *v* 19.0% in the TEC arm; $P < .0001$).

The mean carboplatin dose per patient was AUC 4.9 in both arms, and the mean paclitaxel dose per patient was 170.8 and 169.0 mg/m$^2$ in the TC and TEC arms, respectively. The achieved mean epirubicin dose per patient in the TEC arm was 57.6 mg/m$^2$ according to 87.8% of planned dose-intensity. Overall dose-intensity (ie, received/planned dose for all drugs) was 93.8% and 91.6% in the TC and TEC arm, respectively.

Grade 3/4 hematologic toxicities were significantly more frequent in the TEC arm than in the TC arm, including hemoglobin, leukocytes, neutrophils, and platelets (Table 2). Furthermore, grade 3/4 febrile neutropenia occurred more frequently in the TEC arm than in the TC arm, and patients treated with TEC received more packed RBCs, antibiotics, and G-CSF than patients treated with TC (Table 2).

All grade 3/4 nonhematologic toxicities occurring in more than 1% of patients are listed in Table 3. Some toxicities (specifically nausea, stomatitis/mucositis, vomiting, and infections) were significantly less frequent in the TC arm than in the TEC arm. The occurrence of other nonhematologic toxicities was similar in the two treatment arms except for the experience of pain, which was worse on the TC arm. Notably, we did not find any excessive cardiac toxicity in the TEC arm.

### Tumor Response and Survival

Only 353 patients (27.5%) had measurable disease at study entry and qualified for evaluation of response to treatment. Of those, response to treatment could be assessed in 295 patients (83.6%). A total of 111 (60.0%) of 185 patients in the TC arm had a complete or partial response, compared with 101 (60.1%) of 168 patients in

**Table 2.** Hematologic Toxicities and Associated Supportive Care by Treatment Arm and Toxicity Grade

| | NCI-CTC Grade, % | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC Arm | | | | | | TEC Arm | | | | | | |
| Toxicity | No. | 0 | 1 | 2 | 3 | 4 | No. | 0 | 1 | 2 | 3 | 4 | *P** |
| Hemoglobin | 610 | 8.9 | 54.1 | 31.6 | 4.8 | 0.7 | 612 | 1.8 | 23.5 | 53.8 | 17.7 | 3.3 | < .0001 |
| Platelets | 609 | 57.5 | 31.4 | 7.1 | 2.3 | 1.8 | 612 | 35.3 | 32.0 | 14.7 | 12.6 | 5.4 | < .0001 |
| Transfusion pRBCs | 593 | 91.6 | — | — | 8.4 | — | 606 | 74.4 | — | — | 25.6 | — | < .0001 |
| Leukocytes | 609 | 9.9 | 18.9 | 45.0 | 25.1 | 1.1 | 611 | 3.6 | 7.4 | 23.4 | 53.4 | 12.3 | < .0001 |
| Neutrophils | 553 | 17.5 | 9.8 | 16.8 | 30.7 | 25.1 | 563 | 10.7 | 5.5 | 7.8 | 17.8 | 58.3 | < .0001 |
| Febrile neutropenia | 612 | 97.9 | — | — | 2.0 | 0.2 | 619 | 89.2 | — | — | 10.2 | 0.6 | < .0001 |
| Supportive care | | | | | | | | | | | | | |
| Antibiotics | 593 | 84.1 | — | — | 15.9 | — | 606 | 74.8 | — | — | 25.2 | — | < .0001 |
| G-CSF | 593 | 87.5 | — | — | 12.5 | — | 606 | 72.4 | — | — | 27.6 | — | < .0001 |

NOTE. Maximum grade over all courses within patient. Use of pRBCs, antibiotics and G-CSF was coded as toxicity of grade 3; a grade 0 toxicity was applied otherwise.

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; TC, paclitaxel-carboplatin; TEC, paclitaxel-carboplatin plus epirubicin; No., number of courses in set C and number of patients in set P; pRBCs, packed RBCs; G-CSF, granulocyte colony-stimulating factor; —, not defined.

*Stratified Cochran-Mantel-Haenszel test for differences in the proportions of patients with grades 3/4 toxicity.

**Table 3.** Nonhematologic Toxicities by Treatment Arm and Toxicity Grade

| Toxicity | NCI-CTC Grade, % | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC Arm | | | | | | TEC Arm | | | | | | |
| | No. | 0 | 1 | 2 | 3 | 4 | No. | 0 | 1 | 2 | 3 | 4 | P* |
| Auditory/hearing | 613 | 92.7 | 3.9 | 3.1 | 0.3 | 0.0 | 620 | 93.7 | 3.6 | 1.9 | 0.8 | 0.0 | .2631 |
| Allergic reaction/hypersensitivity | 616 | 86.5 | 8.4 | 2.9 | 1.0 | 1.1 | 626 | 89.9 | 5.4 | 1.8 | 1.3 | 1.6 | .3886 |
| Cardiovascular arrhythmia | 613 | 91.2 | 6.4 | 1.6 | 0.8 | 0.0 | 622 | 88.4 | 7.1 | 3.5 | 0.6 | 0.3 | .7784 |
| Cardiovascular, general | 611 | 97.0 | 2.4 | 0.2 | 0.2 | 0.2 | 618 | 97.2 | 1.9 | 0.7 | 0.2 | 0.0 | .5567 |
| Edema | 613 | 81.1 | 12.9 | 5.4 | 0.7 | 0.0 | 622 | 79.7 | 13.2 | 6.3 | 0.8 | 0.0 | .7539 |
| Alopecia | 612 | 2.9 | 2.1 | 94.9 | — | — | 617 | 3.1 | 1.8 | 95.1 | — | — | — |
| Constipation | 611 | 53.0 | 19.2 | 18.2 | 8.7 | 1.0 | 620 | 49.8 | 16.5 | 21.6 | 11.5 | 0.6 | .1698 |
| Diarrhea | 611 | 76.6 | 16.0 | 4.6 | 2.6 | 0.2 | 622 | 72.2 | 16.4 | 7.7 | 3.4 | 0.3 | .3649 |
| Nausea | 613 | 29.0 | 41.3 | 26.4 | 3.3 | — | 624 | 17.1 | 42.3 | 33.7 | 6.9 | — | .0037 |
| Stomatitis/mucositis | 612 | 76.1 | 18.5 | 5.1 | 0.3 | 0.0 | 621 | 63.3 | 24.6 | 10.1 | 1.9 | 0.0 | .0078 |
| Emesis/vomiting | 611 | 58.1 | 26.0 | 12.9 | 2.5 | 0.5 | 623 | 46.2 | 27.0 | 20.4 | 5.0 | 1.4 | .0040 |
| Infections | 613 | 73.3 | 10.3 | 13.4 | 2.6 | 0.5 | 620 | 62.1 | 11.8 | 17.1 | 8.4 | 0.7 | < .0001 |
| Neuropathy cranial | 613 | 79.4 | — | 19.1 | 1.3 | 0.2 | 620 | 81.3 | — | 18.1 | 0.6 | 0.0 | .1582 |
| Neuropathy sensory | 614 | 35.7 | 38.1 | 22.8 | 3.4 | 0.0 | 620 | 37.4 | 37.7 | 20.8 | 4.0 | 0.0 | .5733 |
| Myalgia | 612 | 46.4 | 33.0 | 16.2 | 4.3 | 0.2 | 621 | 51.1 | 30.8 | 15.3 | 2.9 | 0.0 | .1565 |
| Pain, other | 612 | 46.1 | 24.5 | 18.6 | 10.3 | 0.5 | 620 | 50.0 | 28.1 | 15.3 | 6.0 | 0.7 | .0094 |
| Dyspnea | 612 | 80.1 | — | 16.5 | 2.6 | 0.8 | 623 | 76.6 | — | 18.1 | 4.7 | 0.6 | .1086 |
| Creatinine | 611 | 94.4 | 3.8 | 1.5 | 0.3 | 0.0 | 614 | 94.5 | 4.4 | 1.1 | 0.0 | 0.0 | .1564 |

NOTE. Maximum grade over all courses within patient.
Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; TC, paclitaxel-carboplatin; TEC, paclitaxel- carboplatin plus epirubicin; No., number of patients in set P; —, not defined.
*Stratified Cochran-Mantel-Haenszel test for differences in the proportions of patients with grades 3/4 toxicity.

the TEC arm (Table 4). This difference between treatments was not statistically significant.

There was no imbalance in follow-up between treatment arms; median KM follow-up time was 54 months for both groups and more than 90% of survivors were observed for at least 2 years in both arms. A total of 35 patients (5.5%) in the TC arm and 40 patients (6.2%) in the TEC arm were lost to follow-up; 45 patients (TC, 23 patients; TEC, 22 patients) were lost to follow-up before disease progression.

A total of 968 patients (75.5%) had shown progressive disease or recurrence within the observation period. Median progression-free survival time was 18.4 months (95% CI, 16.2 to 20.2 months) for the TEC arm and 17.9 months (95% CI, 16.3 to 19.7 months) for the TC arm (Fig 2). The stratum-adjusted HR was 0.95 (95% CI, 0.83 to 1.07; stratified log-rank $P = .3342$). In stratum 1, median progression-free survival time was 27.1 months (95% CI, 23.0 to 35.1 months) for the TEC arm and 23.7 months (95% CI, 20.8 to 26.7 months) for the TC arm, corresponding to an HR of 0.91 (95% CI, 0.76 to 1.09; $P = .2955$). In stratum 2, median progression-free survival time was 13.5 months (95% CI, 12.3 to 14.4 months) for the TEC arm and 12.8 months (95% CI, 11.5 to 14.5 months) for the TC arm, corresponding to an HR of 0.97 (95% CI, 0.81 to 1.17; $P = .7560$).

By the end of the observation period, 732 (57.1%) patients had died (Fig 3). The adjusted treatment effect on overall survival was 0.93 (95% CI, 0.81 to 1.08; stratified log-rank $P = .3652$). Median overall survival time was 45.8 months (95% CI, 39.9 to 49.6 months) for the TEC arm and 41.0 months (95% CI, 38.2 to 46.1 months) for the TC arm. The overall survival curves by treatment within each stratum are shown in Figures 4 and 5. In stratum 1, the median overall survival time was 59.8 months (95% CI, 51.7 months to not yet reached) for the TEC arm and 57.0 months (95% CI, 48.7 to 62.5 months) for the

**Table 4.** Clinical Tumor Response to Treatment

| Response | TC Arm | | TEC Arm | | Total | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Unknown | 27 | 14.6 | 31 | 18.5 | 58 | 16.4 |
| CR | 70 | 37.8 | 57 | 33.9 | 127 | 36.0 |
| PR | 41 | 22.2 | 44 | 26.2 | 85 | 24.1 |
| Stable disease | 28 | 15.1 | 15 | 8.9 | 43 | 12.2 |
| Progressive disease | 19 | 10.3 | 21 | 12.5 | 40 | 11.3 |
| Overall response, % | 60.0 | | 60.1 | | 60.1 | |
| 95% CI, % | 52.9 to 67.1 | | 52.7 to 67.5 | | 55.0 to 65.2 | |

NOTE. $\chi^2$ test and Fisher's exact test for differences in the proportions of patients with overall response (CR + PR), $P = .9818$ and $P = 1.0000$; stratified Cochran-Mantel-Haenszel test for differences in the proportions of patients with overall response (CR + PR), $P = .9822$.
Abbreviations: TC, paclitaxel-carboplatin; TEC, paclitaxel-carboplatin plus epirubicin; CR, complete response; PR, partial response.

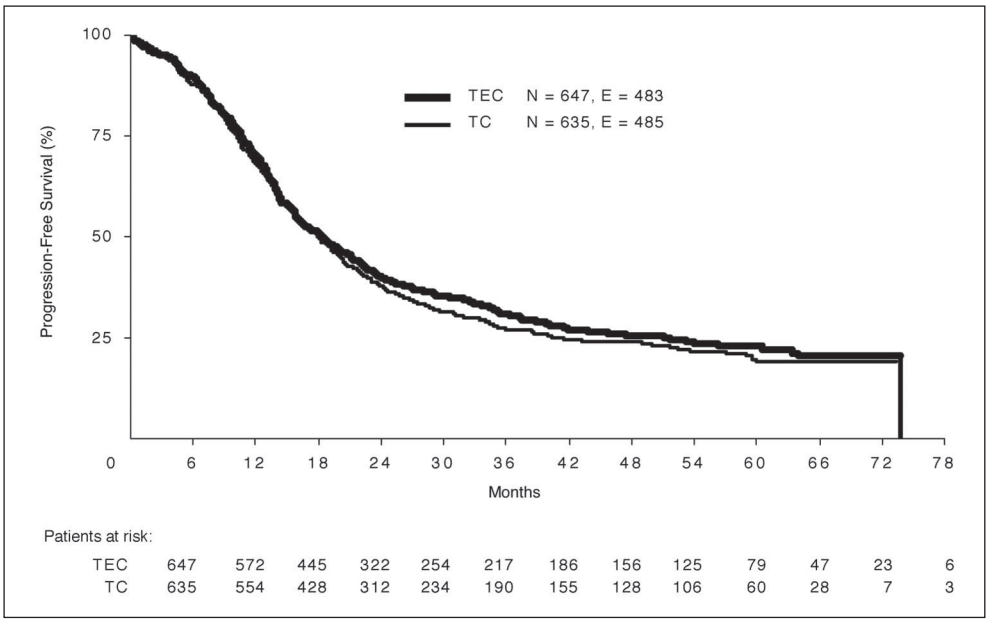


**Fig 2.** Kaplan-Meier estimates of progression-free survival, all randomly assigned patients by treatment. TC, carboplatin-paclitaxel; TEC, carboplatin-paclitaxel plus epirubicin; E, events.

TC arm, corresponding to an HR of 0.91 (95% CI, 0.73 to 1.12; $P = .3683$). In stratum 2, the median overall survival time was 28.7 months (95% CI, 24.9 to 33.7 months) for the TEC arm and 28.1 months (95% CI, 25.3 to 33.7 months) for the TC arm, corresponding to an HR of 0.96 (95% CI, 0.79 to 1.17; $P = .6906$).

### *QoL*

QoL was only analyzed with respect to global health score because the experimental regimen induced significantly more toxicity without adding benefit regarding efficacy. The data for 318 patients receiving TC (68.3% of the German subcohort) and 338 receiving TEC (69.7%) who qualified for QoL analysis showed a slightly better global health score (significant at $P = .04$) at baseline in the TEC arm. In both groups an improvement during chemotherapy was observed, but the TC arm performed significantly better with respect to worst global health score over time points 2 to 4 minus baseline ($P = .0002$) and mean score over time points 2 to 4 minus baseline ($P = .001$). The mean difference between treatments was 8.3 (95% CI, 4.2 to 12.3) for worst minus baseline and 6.4 (95% CI, 2.7 to 10.1) for mean minus baseline.

## DISCUSSION

Despite the progress that had been achieved by the incorporation of paclitaxel into first-line treatment of advanced ovarian cancer, survival rates are still disappointing; eventually, the majority of

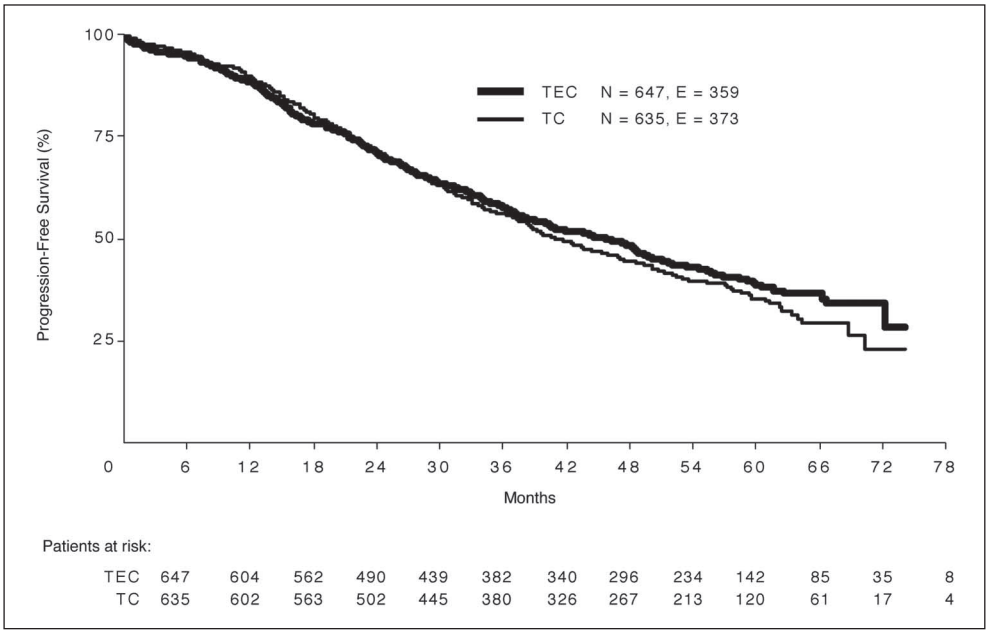


**Fig 3.** Kaplan-Meier estimates of overall survival, all randomly assigned patients by treatment. TC, carboplatin-paclitaxel; TEC, carboplatin-paclitaxel plus epirubicin; E, events.

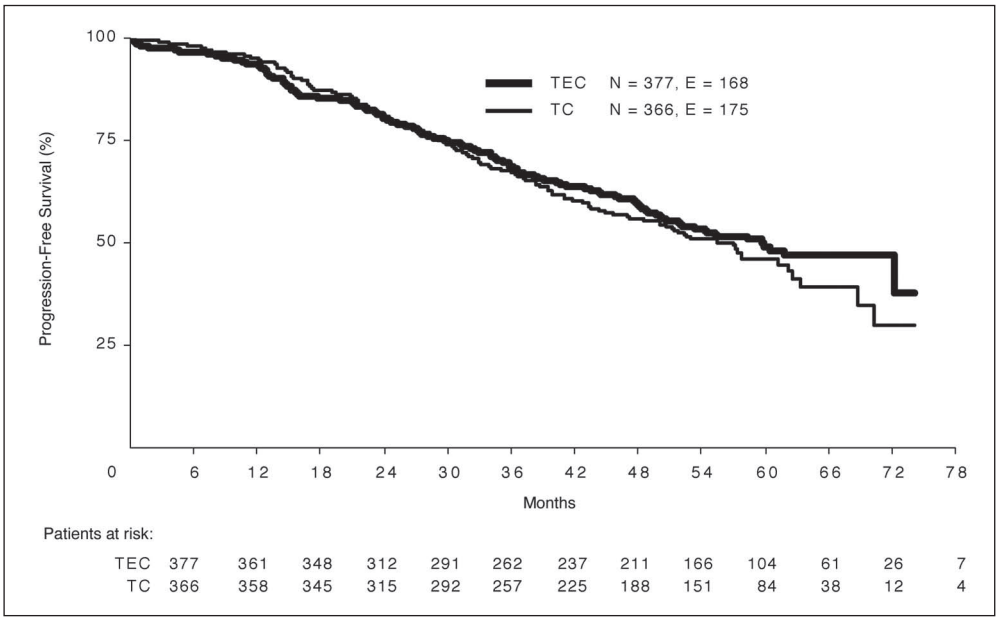


**Fig 4.** Kaplan-Meier estimates of overall survival, all randomly assigned patients by treatment within stratum 1. TC, carboplatin-paclitaxel; TEC, carboplatin-paclitaxel plus epirubicin; E, events.

patients will die as a result of their disease. Therefore, additional efforts to improve efficacy of first-line chemotherapy in ovarian cancer clearly are warranted. One attempt to improve results is adding drugs that are regarded as not completely cross resistant to platinum-paclitaxel combination regimens. Among others, anthracyclines were thought to be candidates for incorporation as a third drug into first-line regimens for advanced ovarian cancer. These assumptions were based on results from meta-analyses and results of smaller studies reporting efficacy in platinum-pretreated relapsed ovarian cancer. However, another large randomized trial comparing single-agent carboplatin with a combination of cisplatin, cyclophosphamide, and doxorubicin failed to show superiority for the anthracycline-containing regimen.[19]

Unfortunately, this trial confirmed the lack of benefit of adding an anthracycline to a more modern platinum-based therapy containing paclitaxel. The incorporation of epirubicin in the TEC regimen evaluated in this study did not show any benefit compared with the two-drug platinum-paclitaxel regimen commonly regarded as standard. The nonsignificant and less than 10% reduction in HR for overall survival was traded off by higher toxicity and lower QoL induced by the anthracycline-containing regimen. Similar observations with respect to progression-free survival have been reported in a confirmatory GCIG trial comparing the same TC combination used in our study with a TEC regimen containing a slightly higher epirubicin dose of 75 mg/m$^2$.[20] A third GCIG trial performed by the US Gynecologic Oncology Group (GOG), the British Medical

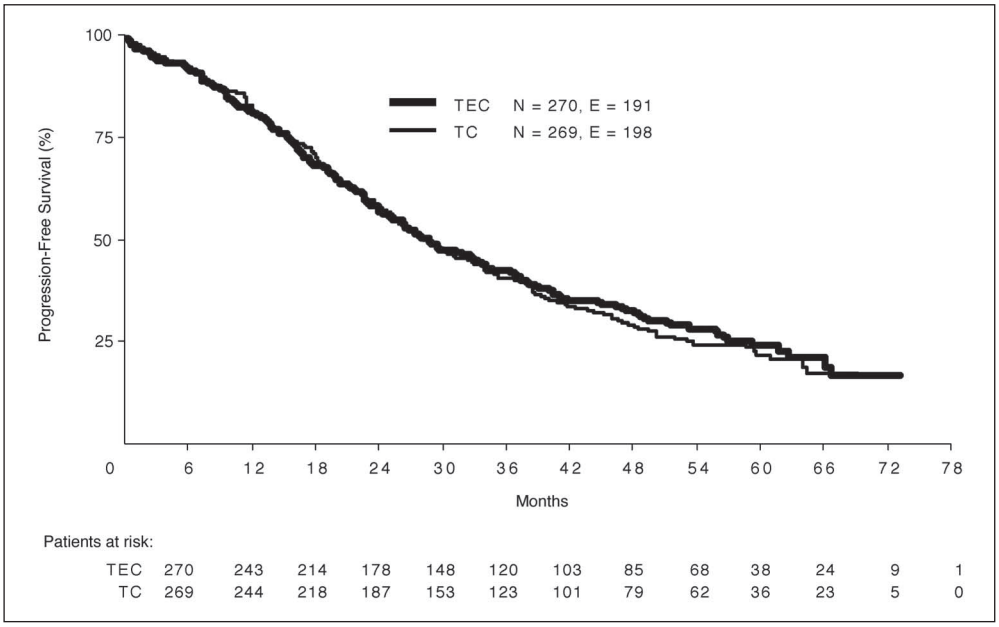


**Fig 5.** Kaplan-Meier estimates of overall survival, all randomly assigned patients by treatment within stratum 2. TC, carboplatin-paclitaxel; TEC, carboplatin-paclitaxel plus epirubicin; E, events.

Research Council, and the Australian-New Zealand GOG is still ongoing and evaluates another anthracycline combination by comparing TC plus liposomal doxorubicin versus TC within a five-arm trial (GOG 182/International Collaborative Ovarian Neoplasm [ICON] -55[21]). However, the optimism regarding the incorporation of anthracyclines has vanished in the light of the negative results currently available from three large trials that have evaluated this question.

The failure of anthracyclines does not prove the failure of the whole concept of incorporating new drugs in first-line regimens in ovarian cancer. The second-generation GCIG trials evaluating three-drug combinations are underway or already completed. Topotecan has been added sequentially to TC in the AGO-OVAR/GINECO trial,[22] and is being evaluated within two ongoing trials as a platinum-topotecan doublet followed by TC (GOG 182/ICON5 and National Cancer Institute of Canada/EORTC/Nordic Society of Gynecologic Oncology Group/Intergroup study). Another GCIG study by AGO-OVAR, GINECO, and Nordic Society of Gynecologic Oncology Group comparing the triple-drug regimen of TC plus gemcitabine versus TC recently has completed accrual with 1,742 patients. Results of this series of studies will gather more evidence if the concept of adding non–cross-resistant drugs to TC will provide any benefit. Although the results of this study seem somewhat disappointing, the development of intergroup collaboration within the field of gynecologic oncology is encouraging. The way intergroup studies are performed can systematically answer important questions within reasonable time frames, and make it more probable that the next generation of questions will be answered more quickly. The latter comprise questions about how to integrate translational research and molecular insights in tumor biology into clinical trials, thus helping to create study scenarios that will allow evaluation of targeted therapies.

## REFERENCES


**1.** McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and Stage IV ovarian cancer. N Engl J Med 334:1-6, 1996

**2.** Piccart MJ, Bertelsen K, James K, et al: Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. J Natl Cancer Inst 92:699-708, 2000

**3.** du Bois A, Lück HJ, Meier, et al: A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 95:1320-1329, 2003

**4.** Ozols RF, Bundy BN, Greer BE, et al: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol 21:3194-3200, 2003

**5.** Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin, and cisplatin chemotherapy of ovarian carcinoma: A meta-analysis—Ovarian Cancer Meta-Analysis Project. J Clin Oncol 9:1668-1674, 1991

**6.** A'Hern RP, Gore ME: Impact of doxorubicin in survival in advanced ovarian cancer. J Clin Oncol 13:726-732, 1995

**7.** Fanning J, Bennett TZ, Hilgers RD: Meta-analysis of cisplatin, doxorubicin, and cyclophosphamide versus cisplatin and cyclophosphamide chemotherapy of ovarian carcinoma. Obstet Gynecol 80:954-960, 1992

**8.** Muggia FM, Hainsworth JD, Jeffers S, et al: Liposomal doxorubicin (doxil) is active against refractory ovarian cancer. Proc Am Soc Clin Oncol 15:287, 1996 (abstr 781)

**9.** Vermorken JB, Kobierska A, van der Burg MEL, et al: High-dose epirubicin in platinum-pretreated patients with ovarian carcinoma: The EORTC-GCCG experience. Eur J Gynaecol Oncol 16:433-438, 1995

**10.** du Bois A, Lück HJ, Bauknecht T, et al: First-line chemotherapy with epirubicin, paclitaxel, and carboplatin (ET-Carbo) for advanced ovarian carcinoma: A phase I/II study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group. J Clin Oncol 17:46-51, 1999

**11.** du Bois A, Combe M, Rochon J, et al: Epirubicin/paclitaxel/carboplatin (TEC) versus paclitaxel/carboplatin (TC) in first-line treatment of ovarian cancer FIGO stages IIB-IV: Mature results of a randomized AGO-GINECO GCIG Intergroup phase III trial. J Clin Oncol 22:450s, 2004 (suppl; abstr 5007)

**12.** International Federation of Gynecology and Obstetrics: Changing in definitions of clinical staging for carcinoma of the cervix and ovary. Am J Obstet Gynecol 156:263-264, 1987

**13.** Calvert AH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989

**14.** Jelliffe RW: Creatinine clearance: Bedside estimate. Ann Intern Med 79:604-605, 1973

**15.** National Cancer Institute: Cancer Therapy Evaluation Program: Common Toxicity Criteria. http://ctep.cancer.gov/reporting/ctc.html

**16.** Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

**17.** Fayers PM, Aaronson NK, Bjordal K, et al: The EORTC QLQ-C30 Scoring Manual (ed 2). Brussels, Belgium, European Organization for Research and Treatment of Cancer, 1999

**18.** World Health Organization.WHO Handbook for Reporting Results of Cancer Treatment. Offset publication 40. Geneva, Switzerland, World Health Organization, 1979

**19.** The ICON and AGO Collaborators: Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The ICON4/AGO-OVAR-2.2 trial. Lancet 361:2099-2106, 2003

**20.** Kristensen GB, Vergote I, Eisenhauer E, et al: First line Treatment of ovarian/tubal/peritoneal cancer FIGO stage IIb-IV with paclitaxel/carboplatin with or without epirubicin (TEC vs TC): A Gynecologic Cancer Intergroup study of the NSGO, EORTC GCG, and NCIC CTG—Results on progression free survival. J Clin Oncol 23:449s, 2004 (suppl; abstr 5003)

**21.** Bookmann MA, Greer BE, Ozols RF: Optimal therapy of advanced ovarian cancer: Carboplatin and paclitaxel vs. cisplatin and paclitaxel (GOG 158) and an update on GOG0 182-ICON5. Int J Gynecol Cancer 13:735-740, 2003

**22.** Pfisterer J, Weber B, du Bois A, et al: Paclitaxel/carboplatin (TC) vs. paclitaxel/carboplatin followed by topotecan (TOP) in first-line treatment of advanced ovarian cancer: Mature results of a Gynecologic Cancer Intergroup phase III trial of the AGO OVAR and GINECO. J Clin Oncol 23:456s, 2005 (suppl; abstr 5007)



### *Acknowledgment*

We thank the staff of AGO-OVAR in Wiesbaden (G. Elser and others, and H.P. Adams) and of GINECO in Paris (Christiane Puelo), the statistical department at the KKS Marburg, and the study monitors (Peter Schantl and others).


### *Appendix*

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

## *Authors' Disclosures of Potential Conflicts of Interest*

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

| Authors | Employment | Leadership | Consultant | Stock | Honoraria | Research Funds | Testimony | Other |
|---|---|---|---|---|---|---|---|---|
| Andreas du Bois | | | | | Bristol-Myers Squibb (A) | Bristol-Myers Squibb (B) | | |
| Uwe Wagner | | | | | Bristol-Myers Squibb (A) | | | |
| Hans-Joachim Lueck | | | Bristol-Myers Squibb (A) | | | | | |
| Jacobus Pfisterer | | | | | Bristol-Myers Squibb (A) | | | |
| Rainer Kimmig | | | | | Bristol-Myers Squibb (A) | | | |
| Eric Pujade-Lauraine | | | | | Bristol-Myers Squibb (A) | Bristol-Myers Squibb (A) | | |

**Dollar Amount Codes** (A) $<$ \$10,000 (B) \$10,000-99,999 (C) $\geq$ \$100,000 (N/R) Not Required

## *Author Contributions*

**Conception and design:** Andreas du Bois, Werner Meier, Sigrid Olbricht, Walther Kuhn, Uwe Wagner, Jacobus Pfisterer, Serban Costa, Willibald Schroeder, Eric Pujade-Lauraine
**Administrative support:** Eric Pujade-Lauraine
**Provision of study materials or patients:** Andreas du Bois, Beatrice Weber, Alain Goupil, Jean-Claude Barats, Walther Kuhn, Hubert Orfeuvre, Uwe Wagner, Hans-Joachim Lueck, Jacobus Pfisterer, Serban Costa, Willibald Schroeder, Eric Pujade-Lauraine
**Collection and assembly of data:** Andreas du Bois, Uwe Wagner, Hans-Joachim Lueck, Jacobus Pfisterer, Rainer Kimmig, Eric Pujade-Lauraine
**Data analysis and interpretation:** Andreas du Bois, Justine Rochon, Werner Meier, Uwe Wagner, Jacobus Pfisterer, Serban Costa, Willibald Schroeder, Eric Pujade-Lauraine
**Manuscript writing:** Andreas du Bois, Justine Rochon, Uwe Wagner, Barbara Richter, Hans-Joachim Lueck, Jacobus Pfisterer
**Final approval of manuscript:** Andreas du Bois, Beatrice Weber, Werner Meier, Alain Goupil, Walther Kuhn, Uwe Wagner, Hans-Joachim Lueck, Jacobus Pfisterer, Serban Costa, Willibald Schroeder, Rainer Kimmig, Eric Pujade-Lauraine